Chapter 1

GENERAL INTRODUCTION

AN INTRODUCTION OF THE METABOLIC SYNDROME

The metabolic syndrome (MetS) is a clustering of medical conditions that reflects overnutrition, sedentary lifestyles, and resultant excess adiposity [1]. Metabolic abnormalities such as abdominal obesity, hyperglycaemia, hypertension and dyslipidaemia often are present together, suggesting that they are not independent of one another and that they may share underlying causes and mechanisms. Having MetS places a subject at a substantially increased risk to develop serious diseases like type 2 diabetes (T2D) and cardiovascular disease (CVD) [1]. Although MetS is a condition mainly seen among individuals with overweight and obesity, even lean individuals may develop features of MetS [2].

Since the 1920s, the clustering of metabolic abnormalities was under the attention of several independent scientists, but they did not address MetS as we know it today [1]. It was until 1988, when the concept of the syndrome was brought to a wider audience by Reaven. He noted that insulin resistance clustered together with glucose intolerance, dyslipidaemia and hypertension, altogether increasing the risk of CVD [3]. The collection of these medical conditions was initially designated *Syndrome X,* although the term *insulin resistance syndrome* was also commonly used [1]. Diagnostic criteria for the syndrome were developed by several health oriented organisations, such as the World Health Organisation (WHO) [4], the European Group for the Study of Insulin Resistance (EGIR) [5], the National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATPIII) [6] and the International Diabetes Federation (IDF) [7]. The precise definition with the contributions of the underlying MetS components is under much debate.

Nowadays, researchers often use the term *Metabolic Syndrome* instead of *Syndrome X*. This term was preferred by the NCEP ATPIII, as it avoids the implication that insulin resistance is the primary or only cause of the metabolic risk factors [6]. The NCEP ATPIII definition is the most widely used definition for MetS, in both clinical medicine and in epidemiological studies, where rapid and simple assessment is important [8]. Accordingly, throughout this thesis the NCEP ATPIII definition was used, which classifies a person with MetS when at least three of the five risk features are present, e.g. abdominal obesity (enlarged waist circumference), elevated blood pressure, fasting plasma glucose and/or triglycerides or reduced HDL cholesterol [6, 9]. Rather than insulin resistance, abdominal obesity is one of the components of MetS. Abdominal obesity is, in contrast to insulin resistance, easily measured and has a clear link with insulin resistance, as well as with the other four metabolic abnormalities [9].

THE EPIDEMIC OF METS

During the past years somewhat varying definitions have been used and some defining values to estimate the prevalence of MetS worldwide have been changed. Not to mention that the composition of the population being studied may vary by sex composition, age, race and ethnicity [1]. Regardless of such details, the obesity epidemic and the ageing population are driving the increasing prevalence of MetS around the world, as well as its consequences like T2D and CVD [10]. The presence of MetS is associated with an approximately fivefold increased risk for incident T2D [11], a twofold increased risk for CVD outcomes and a 1.5-fold increased risk for all-cause mortality [12]. Individuals with MetS are, furthermore, susceptible to other conditions such as polycystic ovary syndrome, fatty liver, gallstones, asthma, sleep disturbances, and some forms of cancer [13].

According to the National Health and Examination Survey (NHANES) 2003-2006, a program of studies among adults and children in the United States, approximately 34% of the studied adult people had MetS using the revised NCEP ATPIII criteria [14]. During the last 15 years the estimated prevalence of MetS increased up to 5% within the NHANES cohort. Grundy et al. [15] reported in his review on the Metabolic Syndrome Pandemic, that based on a series of studies on the occurrence of MetS in Europe, it would be fair to say that approximately one-quarter of the European adult population has MetS. In 2012, the Dutch National Institute for Health and Environment has estimated that among people between 30 and 70 years the prevalence of MetS is 34% in men and 24% in women[1]. Given the high prevalence and severe consequences, MetS is a phenomenon of high public health relevance.

HOW DOES OBESITY AND INSULIN RESISTANCE CONTRIBUTE TO METS?

Although, MetS has received our full attention since 1988, the causative etiology of this syndrome is still not clearly understood. The causes of MetS, and each of its components, is complex since hormonal dysregulation, ageing, proinflammatory state and lifestyle interactions may be involved in the pathophysiological route [13]. Although the estimate on heritability of MetS has not been reported yet, it is clear that all components of the syndrome have a strong genetic basis [16].

Nevertheless, there are two factors which appear to be at the core of the pathophysiology of MetS and its individual components: insulin resistance and abdominal obesity. Though the focus of this dissertation lies on epidemiology, I will provide a short and basic overview.

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1 http://www.rivm.nl/dsresource?objectid=rivmp:76082&type=org&disposition=inline&ns_nc=1

Insulin resistance and abdominal obesity

The term insulin resistance can be broadly defined as a subnormal biological response to normal insulin concentrations. As a result, a higher level of insulin is required to maintain a normal level of glucose in the blood (normoglycaemia) [17]. At normal levels insulin has vasodilator and anti-inflammatory actions [1]. However, in case of insulin resistance, the higher levels of insulin are associated with a higher chance of developing atherosclerosis, as insulin is a type of growth factor, effecting vascular smooth muscle cells, important for the maintenance of plaque stability in atherosclerosis [18]. Disturbed insulin signalling can therefore promote both atherogenesis and advanced plaque progression.

While insulin resistance can develop in the absence of excess fat, it is typically seen in subjects with overweight or obesity. When body fat increases, insulin resistance increases as well [8]. Especially in visceral adipose tissue, e.g. fat surrounding internal organs, free fatty acids (FFA) are released into the circulation. There they find their way to other tissues, such as the liver and skeletal muscle [1].These tissues have a high impact on glucose use and removal of glucose from the circulation. An overload of lipids in these tissues induces insulin resistance [8]. Not only do FFA levels appear to cause insulin resistance, but insulin resistance also appear to cause elevated FFA [1]. Impaired insulin signalling increases lipolysis in adipocytes (fat cells), resulting in an increased turnover of FFA [8]. Due to the overload of FFA in the liver, and the consequent insulin resistance, triglyceride synthesis and storage is increased. The excess triglycerides are released as very low density lipoprotein (VLDL) particles. The resulting hypertriglyceridaemia is furthermore associated with reductions in high density lipoprotein (HDL) and triglyceride enriched low density lipoprotein (LDL), which are also considered factors which promote artherosclerosis [1, 8].

Adipose tissue does not only secrete FFA, but is also an active endocrine organ that releases a variety of hormones and molecules, with either pro-inflammatory or anti-inflammatory properties. In individuals with increased adipose tissue, mainly pro-inflammatory signaling factors are activated, such as high-sensitive C-reactive protein (hs-CRP), interleukin (IL)-6 and Tumor Necrosis Factor-α (TNF-α) [1]. Studies have linked chronic low-grade inflammation to the development of insulin resistance and MetS [19-21].

TREATMENT AND PREVENTION OF METS

Although excessive adiposity is clearly linked to MetS, and both obesity and the individual MetS components might be caused by genetic defects, the high rate at which these conditions develop suggest that environmental factors, such as lifestyle, are just

as much important (causative factors). Since the exact pathophysiological mechanism behind MetS is still not well understood and many factors may be involved, it is unclear whether MetS could be treated in itself. However, the rationale for the implementation of MetS as a diagnosis is to initiate aggressive lifestyle changes with the goal of decreasing T2D and CVD risk by targeting several MetS components at the same time. If lifestyle changes have no desirable result, medical therapy could be used to treat the individual components [22], for instance drugs which lower blood pressure.

Similarly to western societies, the MetS prevalence is rapidly increasing in developing countries, which reflects the transition from a traditional lifestyle to a more Western-like lifestyle [23]. Physical inactivity and a diet high in fats and carbohydrates, as well as smoking, contribute to abdominal obesity and insulin resistance [10]. It is well established that weight loss is the number one treatment for MetS. It may beneficially influence all of the components of the MetS, including excessive adiposity, dyslipidaemia, hypertension, insulin resistance, and hyperglycaemia [1]. However, adherence to weight-loss programs is poor and long-term effects are modest [24, 25]. Epidemiological and clinical studies on the specific responsiveness of a certain individual to lifestyle interventions, such as smoking cessation, modification of alcohol consumption, modifying eating habits and increasing exercise, may contribute to the development of better preventive strategies and treatment of metabolic complications. In this dissertation we will, in part, focus on such lifestyles which may be associated with alterations in metabolic health.

IDENTIFICATION OF THE METABOLICALLY HEALTHY OBESITY PHENOTYPE

The first step in the prevention of MetS and its related morbidities, is tackling the obesity epidemic. This is an absolute necessity since approximately 20% of the entire adult population of the world will be obese by 2030 [26]. To improve intervention and treatment strategies for obesity, we need to accept that obesity is not a uniform condition for which a 'one size fits all' approach might do the trick. In fact, metabolic abnormalities and cardiovascular risk may vary among obese individuals. Individuals with excess adiposity but without major obesity-associated metabolic abnormalities have been identified as metabolically healthy obesity (MHO) [27-29].

Similar to MetS, several definitions are used to define MHO. Some of them are based on the absence of MetS or only some the individual components, while others include the inflammatory status as well. This results in widely varying prevalence estimates of 10-40 % of all obese subjects being metabolically healthy within the same population [30]. Other factors that might account for this wide range of reported prevalences are differences in study design, ethnicity, age-group and sample size [30].

While the metabolically healthy obese are expected to differ from unhealthy obese adults on levels of metabolic risk factors, it is of great interest to identify other physiological and behavioural factors that distinguish healthy obese adults from their unhealthy obese counterparts, as this may reveal modifiable determinants of this preferred state.

THE LIFELINES COHORT STUDY

All studies described in this thesis are based on data from the LifeLines cohort study, a large observational study carried out in the three northern provinces of the Netherlands, i.e. Groningen, Friesland and Drenthe. More than 167,000 persons participate, which is 10% of the Dutch population. With its prospective design, participants will be followed for 30 years, it aims to unravel the influence of environmental and genetic factors (including their interaction) on the development of multifactorial diseases. Between 2006 and 2013 different recruitment strategies were adopted that aimed to include three generations of participants - recruitment of an index population (25 to 49 years of age) via general practitioners, subsequent inclusion of their family members, and online self-registration – which resulted in a low risk of selection bias and a high participation rate. Individuals who were unable to read Dutch or those with limited life expectancy (due to severe illness) were excluded from participation by the general practitioner and were not invited. All participants older than 18 years completed a number of questionnaires covering topics like the occurrence of diseases, general health, medication use, diet, physical activity, personality and many more. They underwent a clinical examination, and biological samples were collected [31, 32].

A comprehensive overview of the data collection can be found in the LifeLines catalogue at www.LifeLines.net. The LifeLines adult population (91.2%, 152,915 persons) was found to be broadly representative for the adults living in the north of the Netherlands [33].

AIMS AND OUTLINE OF THE THESIS

MetS is mainly a consequence of an environment that promotes overweight and obesity. However, not all obese individuals display metabolic abnormalities, and also not all lean individuals present a healthy metabolic profile. The research described in this thesis aimed to provide an update on the prevalence of MetS and MHO, to contribute to a better understanding of the associations between lifestyle factors and metabolic health, and in addition, to examine which aspect of health-related quality of life are influenced by obesity and metabolic health complications.

Chapter 2 within the Healthy Obese Project (HOP) of the BioSHaRE-EU consortium (Biobank Standardisation and Harmonization for Research Excellence in the European Union; www.bioshare.eu), we have assessed the prevalence of MetS and MHO across participating biobanks, covering data of 163,517 people of which 17% were obese. Through a rigorous harmonization process and the use of a unified criteria, we were able to compare key characteristics defining the MHO phenotype across ten cohort studies from seven European countries.

Chapter 3 examines the association between smoking and MetS. Not only MetS and the individual components are explored but also the association between smoking and levels of apolipoproteins (apoA1 and apoB) and lipoprotein particle size (HDL-C/apoA1 and LDL-C/apoB ratios). By taking the latter into account, this chapter also provides a possible patho-physiological mechanism linking smoking to increased CVD risk.

Chapter 4 includes the data of a careful assessment of the combined effects of smoking and alcohol consumption on MetS and its individual components. In addition, we also used data on specific types of alcoholic beverages (beer, wine or spirits and mixed drinks) to obtain the related risk to develop MetS or having a specific component of MetS.

Chapter 5 explores the sex-specific differences in diet and physical activity between the metabolically healthy- and unhealthy obese, taking into account smoking and alcohol use. To this end we have derived obesity-specific dietary patterns, based on self-reported data on 111 items from the Food Frequency Questionnaire.

Chapter 6 presents the associations between obesity-related conditions and HR-QoL. These conditions were grade of obesity with and without T2D, MetS, and inflammation level. Obesity, T2D and MetS are all characterised by inflammation, which have been proposed as being part of the mechanism underlying reduced HR-QoL.

Chapter 7 describes the prevalence of MetS and the individual MetS components in sex, BMI and age combined clusters. Previous studies showed that elevated blood pressure is the most common risk factor in the population. In the definition of MetS, the natural course of increasing blood pressure with ageing has not been taken into account. The strict threshold for elevated blood pressure is used irrespective of age (≥130 mmHg systolic and ≥85 mmHg diastolic). To demonstrate this illogical decision, we additionally applied age-adjusted thresholds to define elevated blood pressure based on the most recent hypertension guideline of the Joint National Committee (JNC).

Chapter 8 provides a summary and discussion of the main results of the thesis, methodological considerations and future perspectives for research on risk factors for CVD and T2D.

REFERENCES

1. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH: The metabolic syndrome. *Endocrine reviews* 2008, 29(7):777-822.
2. Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET: Metabolic and body composition factors in subgroups of obesity: what do we know? *The Journal of clinical endocrinology and metabolism* 2004, 89(6):2569-2575.
3. Reaven GM: Banting Lecture 1988. Role of insulin resistance in human disease. 1988. *Nutrition (Burbank, Los Angeles County, Calif)* 1997, 13(1):65; discussion 64, 66.
4. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic medicine : a journal of the British Diabetic Association* 1998, 15(7):539-553.
5. Balkau B, Charles MA: Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabetic medicine : a journal of the British Diabetic Association* 1999, 16(5):442-443.
6. Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001, 285(19):2486-2497.
7. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome--a new worldwide definition. *Lancet (London, England)* 2005, 366(9491):1059-1062.
8. Huang PL: A comprehensive definition for metabolic syndrome. *Disease models & mechanisms* 2009, 2(5-6):231-237.
9. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr.*et al*: Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005, 112(17):2735-2752.
10. O'Neill S, O'Driscoll L: Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2015, 16(1):1-12.
11. Ford ES, Li C, Sattar N: Metabolic syndrome and incident diabetes: current state of the evidence. *Diabetes care* 2008, 31(9):1898-1904.
12. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ: The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *Journal of the American College of Cardiology* 2010, 56(14):1113-1132.
13. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C: Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004, 109(3):433-438.
14. Ervin RB: Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. *National health statistics reports* 2009(13):1-7.
15. Grundy SM: Metabolic syndrome pandemic. *Arteriosclerosis, thrombosis, and vascular biology* 2008, 28(4):629-636.
16. Song Q, Wang SS, Zafari AM: Genetics of the metabolic syndrome. *Hospital Physician* 2006, 52:51-61.
17. Moller DE, Flier JS: Insulin resistance--mechanisms, syndromes, and implications. *The New England journal of medicine* 1991, 325(13):938-948.
18. von der Thusen JH, Borensztajn KS, Moimas S, van Heiningen S, Teeling P, van Berkel TJ, Biessen EA: IGF-1 has plaque-stabilizing effects in atherosclerosis by altering vascular smooth muscle cell phenotype. *The American journal of pathology* 2011, 178(2):924-934.
19. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B: Recent advances in the relationship between obesity, inflammation, and insulin resistance. *European cytokine network* 2006, 17(1):4-12.
20. Elks CM, Francis J: Central adiposity, systemic inflammation, and the metabolic syndrome. *Current hypertension reports* 2010, 12(2):99-104.
21. Maury E, Brichard SM: Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Molecular and cellular endocrinology* 2010, 314(1):1-16.

22. Grundy SM: Metabolic syndrome: a multiplex cardiovascular risk factor. *The Journal of clinical endocrinology and metabolism* 2007, 92(2):399-404.
23. Kassi E, Pervanidou P, Kaltsas G, Chrousos G: Metabolic syndrome: definitions and controversies. *BMC medicine* 2011, 9:48.
24. Douketis JD, Macie C, Thabane L, Williamson DF: Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. *International journal of obesity (2005)* 2005, 29(10):1153-1167.
25. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, Bowman JD, Pronk NP: Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *Journal of the American Dietetic Association* 2007, 107(10):1755-1767.
26. Kelly T, Yang W, Chen CS, Reynolds K, He J: Global burden of obesity in 2005 and projections to 2030. *International journal of obesity (2005)* 2008, 32(9):1431-1437.
27. Karelis AD, Brochu M, Rabasa-Lhoret R: Can we identify metabolically healthy but obese individuals (MHO)? *Diabetes & metabolism* 2004, 30(6):569-572.
28. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, Sladek R, Rabasa-Lhoret R: Characterizing the profile of obese patients who are metabolically healthy. *International journal of obesity (2005)* 2011, 35(7):971-981.
29. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, Balletshofer B, Machicao F, Fritsche A, Haring HU: Identification and characterization of metabolically benign obesity in humans. *Archives of internal medicine* 2008, 168(15):1609-1616.
30. Phillips CM: Metabolically healthy obesity: definitions, determinants and clinical implications. *Reviews in endocrine & metabolic disorders* 2013, 14(3):219-227.
31. Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, van Dijk F, van Zon SK, Wijmenga C, Wolffenbuttel BH*et al*: Cohort Profile: LifeLines, a three-generation cohort study and biobank. *International journal of epidemiology* 2015, 44(4):1172-1180.
32. Stolk RP, Rosmalen JG, Postma DS, de Boer RA, Navis G, Slaets JP, Ormel J, Wolffenbuttel BH: Universal risk factors for multifactorial diseases: LifeLines: a three-generation population-based study. *European journal of epidemiology* 2008, 23(1):67-74.
33. Klijs B, Scholtens S, Mandemakers JJ, Snieder H, Stolk RP, Smidt N: Representativeness of the LifeLines Cohort Study. *PloS one* 2015, 10(9):e0137203.